

Application Serial No. 10/639,076
Amendment dated April 13, 2005
Reply to Office Action of January 13, 2005

This listing of claims replaces all previous versions and listings of claims in the application:

Listing of Claims:

1. (Currently amended) A peptide comprising the sequence

Trp₁-Glu₁-Val-Leu-Cys₁-Trp₂-Thr₁-Trp₃-Glu₂-Thr₂-Cys₂-Glu₃-Arg

(SEQ ID NO: 4),

wherein between zero and eight amino acids of SEQ ID NO: 4 are substituted according to the following:

Trp₁ is Trp, Phe, Tyr, Leu, Ile, Met, Val or Ala;

Glu₁ is any amino acid;

Val is Val, Trp, Phe, Tyr, Leu, Ile, Met or Ala;

Leu is Leu, Trp, Phe, Tyr, Ile, Met, Val or Ala;

Trp₂ is Trp, Phe, Tyr, Leu, Ile, Met, Val or Ala;

Thr₁ is any amino acid;

Trp₃ is Trp, Phe, Tyr, Leu, Ile, Met, Val or Ala;

Glu₂ is any amino acid;

Thr₂ is any amino acid;

Glu₃ is any amino acid;

Arg is Arg, Lys, Leu, Trp, His, Met or Ile; and wherein the peptide binds FVII/FVIIa in an *in vitro* assay.

2. (Previously Presented) The peptide of claim 1,

wherein between zero and eight amino acids of SEQ ID NO: 4 are substituted according to the following:

Trp₁ is Trp, Phe or Leu;

Glu₁ is any amino acid;

Val is Val or Ile;

Leu is Leu, Ile, Met, Val or Ala;

Trp₂ is Trp, Phe, Tyr, Leu or Met;

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Thr₁ is any amino acid;

Trp₃ is Trp;

Glu₂ is any amino acid;

Thr₂ is any amino acid;

Glu₃ is any amino acid;

Arg is Arg, Lys, Leu or Trp.

3. (Original) The peptide of claim 2 having an IC₅₀ for FVII/FVIIa of less than 1 μ M.
4. (Original) The peptide of claim 3 having an IC₅₀ for FVII/FVIIa of less than 100 nM.
5. (Original) The peptide of claim 4 having an IC₅₀ for FVII/FVIIa of less than 10 nM.
6. (Currently Amended) The peptide of claim [[5]] 1 which ~~binds FVII/FVIIa and~~ inhibits FVIIa activity.
7. (Original) The peptide of claim 6 which blocks an activity associated with FVIIa selected from the group consisting of activation of FVII, activation of FIX and activation of FX.
8. (Original) The peptide of claim 7 which inhibits activation of FX.
9. (Original) The peptide of claim 8 having an IC₅₀ for inhibiting FX activation of less than 10 μ M.
10. (Original) The peptide of claim 9 having an IC₅₀ for inhibiting FX activation of less than 100 nM.
11. (Original) The peptide of claim 10 having an IC₅₀ for inhibiting FX activation of less than 5 nM.

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12. (Currently Amended) The peptide of claim [[11]] 1, having the following formula:
 $X_i\text{-Trp}_1\text{-Glu}_1\text{-Val-Leu-Cys}_1\text{-Trp}_2\text{-Thr}_1\text{-Trp}_3\text{-Glu}_2\text{-Thr}_2\text{-Cys}_2\text{-Glu}_3\text{-Arg-X}_k$
wherein X_i is absent or is between 1 and 100 amino acids; and X_k is absent or between 1 and 100 amino acids.
13. (Original) The peptide of claim 12 wherein X_i and X_k are between 1 and 50 amino acids.
14. (Original) The peptide of claim 13 wherein X_i and X_k are between 1 and 10 amino acids.
15. (Currently amended) The peptide of claim 14 having the formula
 $Xaa_1\text{-Xaa}_2\text{-Trp}_1\text{-Glu}_1\text{-Val-Leu-Cys}_1\text{-Trp}_2\text{-Thr}_1\text{-Trp}_3\text{-Glu}_2\text{-Thr}_2\text{-Cys}_2\text{-Glu}_3\text{-Arg-Xaa}_{16}\text{-Xaa}_{17}\text{-Xaa}_{18}$, wherein between zero and eight amino acids are substituted according to the following:
- Xaa₁ is an amino acid;
 - Xaa₂ is an amino acid;
 - Trp₁ is Trp, Phe, Leu, Ala, Met or Val;
 - Glu₁ is an amino acid;
 - Val is Val, Ile, Ala, Trp or Tyr;
 - Leu is Leu, Ile, Met, Val or Ala;
 - Trp₂ is Trp, Phe, Leu, Met, Ala or Val;
 - Thr₁ is an amino acid ;
 - Trp₃ is Trp, Phe, Met or Tyr;
 - Glu₂ is an amino acid;
 - Thr₂ is an amino acid;
 - Glu₃ is an amino acid except proline;
 - Arg is Arg, Lys, Leu, Trp, His or Met;
 - Xaa₁₆ is an amino acid;
 - Xaa₁₇ is an amino acid; and
 - Xaa₁₈ is an amino acid.

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16. (Previously Presented) The peptide of claim 15, wherein
Trp₁ is Trp, Phe, Leu or Ala;
Val is Val, Ile or Ala; and
Trp₂ is Trp, Phe, Leu, Met or Ala.
17. (Previously Presented) The peptide of claim 16, wherein
Trp₁ is Trp, Phe, or Leu;
Val is Val or Ile;
Leu is Leu, Ile, Met or Val;
Trp₂ is Trp, Phe, Leu or Met;
Trp₃ is Trp; and
Arg is Arg, Lys, Leu or Trp.
18. (Currently Amended) The peptide of claim 17, wherein $\text{Trp}_2\text{-Thr}_1\text{-Trp}_3\text{-Glu}_2\text{-Thr}_2$ is
 $\text{-Trp-Thr-Trp-Glu-Thr-}$ (SEQ ID NO:100).
19. (Withdrawn) A method of inhibiting FVIIa activity comprising the step of:
a) contacting FVIIa with a peptide of claim 1 in the presence of tissue factor and under conditions which allow binding of the compound to FVIIa to occur.
20. (Withdrawn) A method for selecting a compound which blocks FVII/FVIIa activation of FX comprising the steps of:
(1) contacting FVII/FVIIa with a compound of claim 1 in the presence and absence of a candidate molecule under conditions which allow specific binding of the compound of claim 1 to FVII/FVIIa to occur;
(2) detecting the amount of specific binding of the compound of claim 1 to FVII/FVIIa that occurs in the presence and absence of the candidate compound wherein the amount of binding in the presence of the candidate compound relative to the amount of binding in the absence of the candidate molecule is indicative of the ability of the candidate compound to block FVII/FVIIa activation of FX.

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21. (Withdrawn) A method of inhibiting the activation of FX comprising contacting FVII/FVIIa with a compound that prevents the interaction of FVII/FVIIa with a compound of claim 1.
22. (Withdrawn) The method of inhibiting the activation of FX of claim 21 comprising contacting FVII/FVIIa with a compound that prevents the interaction of FVII/FVIIa with SEQ ID NO: 4.
23. (Withdrawn) The method of claim 22, wherein the contacting occurs *in vivo*.
24. (Withdrawn) The method of claim 22, wherein the contacting occurs *in vitro*.
25. (Withdrawn) A method of treating a TF/FVIIa mediated disease or disorder in a host in need thereof comprising administering to the host a therapeutically effective amount of a compound of claim 1.
26. (Withdrawn) A method of treating a TF/FVIIa mediated disease or disorder in a host in need thereof comprising administering to the host a therapeutically effective amount of the peptide of claim 1.
27. (Cancelled)
28. (Currently amended) A pharmaceutical composition comprising the peptide of claim 27 1 and a pharmaceutically acceptable carrier.
29. (Original) The composition of claim 28, which is suitable for inhalation.
30. (Previously Presented) The composition of claim 29, which is dry powder.

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31. (Previously Presented) The composition of claim 29, which is a liquid.
32. (Currently amended) A disulfide-constrained peptide comprising the formula
Trp₁-Glu₁-Val-Leu-Cys₁-Trp₂-Thr₁-Trp₃-Glu₂-Thr₂-Cys₂-Xaa-Arg, wherein between zero
and five amino acids are substituted according to the following:
Leu is substituted with Met, Ile, or Val;
Thr₁ is substituted with Ala, Ser, Glu, Gly, Asp, or Gln;
Thr₂ is Gly, Asp, Gln, Ala, Ser, Glu, Thr, Val, or Asn; and
Xaa is any amino acid; and
Arg is Leu, Ser or Trp.
33. (Currently Amended) A The disulfide-constrained peptide of claim 32, wherein the
peptide comprises:
Trp₁-Glu₁-Val-Leu-Cys₁-Trp₂-Thr₁-Trp₃-Glu₂-Thr₂-Cys₂-Xaa-Arg, wherein between zero
and five amino acids are substituted according to the following:
Leu is substituted with Met, Ile, or Val;
Thr₁ is substituted with Ala, Ser, Glu, Gly, Asp, or Gln;
Thr₂ is Gly, Asp, Gln, Ala, Ser, Glu, Thr, Val, or Asn; and
Xaa is any amino acid.
34. (Currently Amended) A The disulfide-constrained peptide of claim 32, wherein the
peptide comprises:
SAEWEVLCWTWEGCGSVGLV (SEQ ID NO:1) TF53;
SEEWEVLCWTWEDCRLEGLE (SEQ ID NO:2) TF57;
WEVLCWTWEDCER (SEQ ID NO:3) TF 64;
WEVLCWTWETCER (SEQ ID NO:4) TF 65;
WEVVCWTWETCER (SEQ ID NO:5) TF 66;
EWEVLCWTWETCERGE (SEQ ID NO:17) TF99;
EEWEVLCWTWETCERGEG (SEQ ID NO:18) TF100; or
EEWEVLCWTWETCER (SEQ ID NO:23) TF183.

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35. (new) The disulfide-constrained peptide of claim 34, wherein the peptide comprises:
SAEWEVLCWTWEGCGSVGLV (SEQ ID NO:1) TF53.
36. (new) The disulfide-constrained peptide of claim 34, wherein the peptide comprises:
SEEWEVLCWTWEDCRLEGLE (SEQ ID NO:2) TF57.
37. (new) The disulfide-constrained peptide of claim 34, wherein the peptide comprises:
WEVLCWTWEDCER (SEQ ID NO:3) TF 64.
38. (new) The disulfide-constrained peptide of claim 34, wherein the peptide comprises:
WEVLCWTWETCER (SEQ ID NO:4) TF65.
39. (new) The disulfide-constrained peptide of claim 34, wherein the peptide comprises:
WEVVCWTWETCER (SEQ ID NO:5) TF 66.
40. (new) The disulfide-constrained peptide of claim 34, wherein the peptide comprises:
EWEVLCWTWETCERGE (SEQ ID NO:17) TF99.
41. (new) The disulfide-constrained peptide of claim 34, wherein the peptide comprises:
EEWEVLCWTWETCEREGEG (SEQ ID NO:18) TF100.
42. (new) The disulfide-constrained peptide of claim 34, wherein the peptide comprises:
EEWEVLCWTWETCER (SEQ ID NO:23) TF183.
43. (new) The peptide of claim 1,12 ,or 32, wherein the N terminal amino acid is modified,
the C terminal amino acid is modified, or both the N and C terminal amino acids are modified.